REMARKS

Entry of this Amendment is proper under 37 C.F.R. 1.116, because the Amendment places the application in condition for allowance for the reasons discussed herein; does not introduce any new claims; does not raise any new issue requiring further search and/or consideration because the amendments amplify issues previously discussed throughout prosecution, and places the application in better form for an appeal should an appeal be necessary.

As noted in the Office Action Summary, claims 10-20, 25-31, 86, 89, 105, 107, 117, 118, and 124-139 are pending. Claims 10-20, 25-31, and 86 stand withdrawn. Claims 89, 124-129, 131-133, and 136-137 are canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation directed to any subject matter canceled herein.

Claims 105, 107, 117, and 130 are amended herein. Basis for the amendments may be found throughout the specification and claims as filed, especially in claims 129, 131, and 136. Thus, no prohibited new matter is presented herein.

Rejections Under 35 U.S.C. § 112, first and second paragraphs

Claims 89, 105, 117, 128, 133, 134, 137 and 138 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite. Claims 89, 105 and 117 are purportedly vague, as the Office states that the metes and bounds "nononcogenic variants" of E6 and/or E7 cannot be discerned. Claims 89, 128, 133, and 137 are deleted herein. Claims 105 and 117 are amended herein to recite

specific nononcogenic variants previously recited in claim 136. Thus, Applicants request that this rejection be withdrawn.

Claims 89, 105, 117, 128, 133, 134, 137 and 138 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly failing to comply with the written description requirement. The Office argues that the specification does not teach the structural elements of the nononcogenic variants of E6 and/or E7. As noted above, claims 89, 128, 133, and 137 are deleted herein. Claims 105 and 117 are amended herein to recite specific nononcogenic variants.

In light of the above amendments, Applicants request that the rejections under 35 U.S.C. § 112 be withdrawn.

Claim Rejections Under 35 U.S.C. § 103

Claims 89 and 124-128 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Lowy *et al.* (WO 96/11274) ("Lowy"), Galloway (*Infectious Agents and Disease*, 1994, 3: 187-193) ("Galloway"), Crook *et al.* (*Cell.* 1991, 67: 547-556) ("Crook") and Munger *et al.* (*EMBO Journal*, 1989, 8: 4099-4105) ("Munger"). As claims 89 and 124-128 are canceled herein, this rejection is moot.

Claims 105, 107 and 129-135 stand rejected under 35 U.S.C. § 103(a) as purportedly being unpatentable over Lowy, Galloway, Crook and Munger and further in view of Bubenik (March 1996 *Intl. J. Oncol.* 8: 477-481)("Bubenik"). Applicants respectfully traverse.

For a *prima facie* case of obviousness, the following three requirements must be met. First, the prior art relied upon, coupled with the knowledge generally

available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine the reference with another reference. Second, the proposed modification must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Third, the prior art reference must teach or suggest all the limitations of the claims. The teachings or suggestions as well as the expectation of success must come from the prior art and not from applicant's disclosure. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *Amgen, Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); and *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Applicant respectfully submits that these criteria have not been met in the present Office Action.

First, Applicants note that the present claims, as amended herein, are directed to methods of treating HPV-associated dysplasia or cervical cancer by administering a composition. The composition consists of nononcogenic variants of the E6 and E7 polypeptide and native L1 and L2 polypeptides, as well as a polypeptide having an immunostimulatory activity which is either IL-7 or IL-2.

Addressing the references, Lowy discloses a method of preventing or treating papillomavirus infection and papillomavirus-induced lesions relying on the use of chimeric virus like particles (VLP). The chimeric VLPs are comprised of a self assembled L1 polypeptide and a fusion product between L2 and an early papillomavirus polypeptide. The incorporation of the early polypeptide into the L2 polypeptide causes the presentation of the early epitopes at the surface of the VLP. Thus, Applicants again note Lowy disclose and teach the skilled artisan that the

presentation of the early polypeptides at the surface of the VLP is required in order to achieve the desired therapeutic benefit.

To this end, the skilled artisan would not combine Lowy with Galloway. It is well known in the art that antitumoral responses require cell-mediated immunity. Applicants draw the Office's attention to the second paragraph of Galloway on page 190. Galloway states that "[W]hile neutralizing antibodies may be useful in preventing infection, the cell-mediated immune response is likely to be important in controlling reactivation and regression of infections". Lowy fails to provide any data supporting the effective protection of the chimeric VLPs against HPV-associated dysplasia or tumors. Instead, Lowy teaches that the chimeric L2-E7 fusion becomes incorporated into the L1-based VLPs, and that the E7 moiety is indeed presented at the VLP surface, because rabbits inoculated with such chimeric VLPs produce anti-E7 antibodies.

In fact, apart from detecting neutralizing anti-E7 antibodies in immunized animals and merely demonstrating prophylactic protection against subsequent papillomavirus infection, Lowy does not demonstrate any therapeutic effect when the chimeric VLP particles present E7 at their surface. Examples 10-13 of Lowy describe experimental procedures that may be attempted in order to administer chimeric VLPs to an animal, and discusses how one might attempt to evaluate the resulting response. However, Lowy does not provide any experimental data that actually supports the ability of these chimeric VLPs to treat papilloma-induced cancers. Rather, the teaching of Lowy is merely prophetic.

Galloway does not remedy to the deficiencies of Lowy such that the cited references, in combination, disclose the present invention or provide an expectation

of success upon combination. Galloway discussses therapeutic compositions which have resulted in an antitumor response. Such compositions include (i) L2 and E7 fusion proteins, (ii) E6 or E7 expressing fibroblasts or (iii) vaccinia virus expressing E5, E6 or E7 (*see* first paragraph at the tope of page 191 of Galloway). Therefore, Galloway alone or in combination with Lowy, fails to teach or even to suggest the composition including L1, L2, E6 and E7 papillomavirus polypeptides and an immunostimulatory polypeptide that is used for therapeutically treating HPV-associated lesions.

Bubenik fails to teach or suggest the present method as claimed in the present invention, based on the direct administration of a composition comprising L1, L2, E6 and E7 papillomavirus polypeptides and IL-2. Instead, Bubenik disclose the separate administration of the immunogenic composition *(i.e.,* irradiated tumor cells) and IL-2. In fact, Bubenik discloses that huge quantity of IL-2 are necessary to augment the immune response to HPV-16 infected cells (*i.e.*, 20 injections of IL-2 doses are necessary to provide an adjuvant effect). Therefore, Bubenik fails to provide a reasonable expectation of success to the skilled artisan with respect to the direct administration of a composition that includes L1, L2, E6 and E7 papillomavirus polypeptides and IL-2. Combining Bubenik with the other cited references does not teach or suggest the present invention.

Thus, there is no incentive in Lowy, taken with Galloway, Munger, and Bubenik to treat papillomavirus-associated dysplasia and tumors by administering a mixture of early E6, E7, L1 and L2 papillomavirus polypeptides, and especially in a non-fused form, together with a polypeptide having an immunostimulatory activity which is either IL-7 or IL-2.

Claims 117, 118 and 136-139 stand rejected under 35 U.S.C. § 103(a) as purportedly being unpatentable over Galloway, Crook and Munger et al. and further in view of Bubenik.

As discussed above Galloway is merely a review article regarding a series of therapeutic vaccinations, based upon administration of individual early papillomavirus polypeptides (*see* page 191), using a cellular approach (*i.e.,* inoculation of fibroblasts expressing either rHPV-16 E6 or E7; and inoculated mice could reject challenge by a melanoma cell line expressing the HPV oncogenes) a peptidic approach (*i.e.,* a peptide from HPV-16 E7 was found to protect mice from a syngeneic HPV-16 tumor in an MHC-restricted fashion) and finally gene transfer (*i.e.,* vaccinia virus recombinants expressing the BPV E5, E6 or E7 genes could retard the development of a BPV-transformed cell line in syngeneic rats).

Galloway does not provide teaching and motivation for the skilled artisan to use the recited composition (*i.e.,* a combination of E6 and E7 papillomavirus polypeptides). Galloway fails to even disclose the use of IL-2.

Bubenik discloses a therapeutic strategy which involves administration of HPV-16 infected tumor cells followed by repeated injection of recombinant IL-2 and thus does not remedy Galloway nor does Munger. The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

The references, in combination, fail to provide motivation to arrive at the present invention or an expectation of success. Applicants submit that the skilled artisan would not have been motivated to treat papillomavirus-induced dysplasia or cervix cancers by administering E6 and E7 papillomavirus polypeptides and IL-2 in

light of Galloway teaching the use of individual early papillomavirus polypeptide and further in view of Bubenik disclosing a cellular therapy requiring administration of irradiated tumor cells and numerous injections of IL-2.

For at least these reasons, the Applicant maintains that no *prima facie* case for obviousness has been established, and respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

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By: _____
Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

VA 726597.1